# American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease

*This technical review addresses the state of evidence for celiac disease epidemiology, detection by serologic testing, diagnosis by biopsy, treatment, and outcome. It updates the previous American Gastroenterological Association (AGA) Institute technical review on celiac disease published in 2001.*

**See CME quiz on page 1972.**

Celiac disease is a unique disorder that is both a food intolerance and autoimmune disorder. Celiac disease can be defined as a permanent intolerance to the storage proteins from wheat rye and barley, herein after referred to as "gluten." It is characterized by a chronic inflammatory state of the proximal small intestinal mucosa that heals when foods containing gluten are excluded from the diet and returns when these foods are reintroduced. Complex adaptive and innate immune reactions result in chronic inflammation of the mucosa and a panoply of structural and functional changes. There is atrophy of the small intestinal villi, deepening of the crypts, and infiltration of the lamina propria and intraepithelial compartments with chronic inflammatory cells. The functional changes include decreased digestion of food, decreased absorption of macronutrients and micronutrients, and increased net secretion of water and solute. Other consequences of chronic inflammation such as ulceration or stricturing may occur, although much less frequently. Extraintestinal manifestations affect many organ systems.

## Pathology

Although celiac disease has consequences for many organs, the site of maximum impact is the proximal small intestine, which is where dietary gluten first encounters the mucosal immune system. Over the past 50 years, celiac disease has become defined by this small intestinal damage. Our understanding of the spectrum of injury and its consequences has increased substantially over the past several years. There are varying degrees of inflammation and architectural changes that occur at presentation and recur progressively when treated and healed celiac disease is rechallenged with gluten. A progression of mucosal injury was first described by Marsh et al and has evolved into a grading of histologic damage that reflects the varying degrees of villous atrophy and inflammatory change (Table 1 and Figure 1). Most symptomatic patients when diagnosed with celiac disease will have changes in villous morphology with some degree of atrophy. The finding of increased intraepithelial lymphocytes, without any other changes (Marsh grade 1), is not specific for celiac disease.[1,2] While it has been assumed that many of these subjects are asymptomatic, that is not necessarily true because some of these patients may have diarrhea that resolves with a gluten-free diet (GFD).[3] Further, because only ultramicroscopic changes have been described in some symptomatic subjects with a positive endomysial antibody (EMA), and those symptoms resolved with the exclusion of dietary gluten, minimal lesions may be associated with symptoms, although this is unusual.[4,5] These minor degrees of damage are more commonly seen with dermatitis herpetiformis, which is an extremely itchy blistering rash that affects extensor surfaces and, like celiac disease itself, is dependent on the consumption of gluten.[6]

## Pathogenesis

Recent information has illuminated our understanding of the basic mechanisms that lead to the development of celiac disease. We briefly summarize these advances to provide a pathophysiologic context for the more detailed analysis of questions of immediate importance to clinical practice. Furthermore, such pathophysiologic insights into the disease suggest potential therapeutic alternatives that ultimately may be substitutes or adjuncts to the GFD. A full review of the processes that lead to the development of this unique disease is beyond this clinically focused document. It is clear that celiac disease occurs because of the interaction between derivatives of dietary grains, immune factors, and an individual's genetic makeup.

### *Gluten*

Celiac disease is activated by the dietary ingestion of gluten. Gluten, in the context of celiac disease, encompasses the storage proteins derived from the cultivated grasses: wheat, barley, and rye. These proteins are enriched in glutamines and prolines and undergo partial but incomplete digestion in the upper gastrointestinal tract, resulting in a wide variety of native peptide derivatives. The specific peptide sequences that can elicit immune responses are quite variable and occur throughout the storage proteins of all 3 grains. Of interest is a 33–amino acid peptide sequence from an $\alpha$-gliadin that survives intestinal digestion intact, and this peptide contains several motifs that are especially immunogenic to the celiac intestine.[7] It is the persistence of highly immunogenic peptides, of which the 33 amino acid is one example, that seems to be crucial to the development of the immune response to gluten in the

*Abbreviations used in this paper:* AGA, antigliadin antibodies; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DM1, type 1 diabetes mellitus; EMA, endomysial antibodies; GFD, gluten-free diet; GP, guinea pig liver; HU, human umbilical cord; IDA, iron deficiency anemia; ME, monkey esophagus; NHL, non-Hodgkin's lymphoma; PPV, positive predictive value; SDS, standard deviation score; SIR, standardized incidence ratio; SMR, standardized mortality rate; tTG, tissue transglutaminase; tTGA, tissue transglutaminase antibody.


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**Table 1.** Histologic Grading in Celiac Disease

| | |
|---|---|
| Marsh 0 | Normal mucosal and villous architecture |
| Marsh I | Infiltrative |
| | Normal mucosal and villous architecture |
| | Increased numbers of intraepithelial lymphocytes |
| Marsh II | Hyperplastic |
| | Similar to above, but with enlarged crypts and with increased crypt cell division |
| Marsh III | a. Partial villous atrophy |
| | Shortened blunt villi |
| | Mild lymphocyte infiltration |
| | Enlarged hyperplastic crypts |
| | b. Subtotal villous atrophy |
| | Clearly atrophic villi, but still recognizable |
| | Enlarged crypts whose immature epithelial cells are generated at an increased rate |
| | Influx of inflammatory cells |
| | c. Total villous atrophy |
| | Complete loss of villi |
| | Severe crypt hyperplastic, and infiltrative inflammatory lesion |
| Marsh IV | Hypoplastic |
| | Total villous atrophy |
| | Normal crypt depth, but hypoplasia |
| | Normal intraepithelial lymphocyte count |
| | Many feel this does not exist and represents severe malnutrition |

intestine of patients with celiac disease. These peptides pass through the epithelial barrier and reach antigen-presenting cells in the lamina propria.

### *Mucosal Immune Response*

Immune responses to gluten in celiac disease activate an inflammatory reaction characterized by infiltration of the lamina propria and the epithelial compartments with chronic inflammatory cells and progressive architectural changes in the mucosa. Immunogenic peptides rich in glutamine and proline elicit a chronic immune response that is initiated and mediated by both the innate and adaptive arms of the mucosal immune system.

**Adaptive response.** The adaptive response is mediated by gluten-reactive $CD4^+$ T cells in the lamina propria that recognize certain gluten-derived peptides when they are presented by the HLA class II molecules DQ2 or DQ8. These cells then produce proinflammatory cytokines. Although native peptides can elicit a response, if certain glutamine residues in the gluten peptides undergo deamidation, thereby forming a negatively charged glutamic acid residue, the resulting peptide can bind in the binding groove of the DQ2 or DQ8 molecules with a higher affinity. It has been shown that tissue transglutaminase (tTG) in the intestine can perform this targeted deamidation. T cells activated by gluten produce interferon gamma and other proinflammatory cytokines. During the resulting inflammatory cascade, the release of metalloproteinases and other tissue-damaging mediators results in villous injury and the associated crypt hyperplasia characteristic of fully developed celiac disease.

**Innate response.** Gluten-derived peptides can also activate an innate response. The innate response is typified by increased expression of interleukin-15 by enterocytes, which drives the activation of populations of intraepithelial lymphocytes that express the NK marker (NKG2D).[1] These cells are then able to recognize and kill enterocytes that express stress molecules (MICA) on their surface.[8,9] Additionally, the innate response results in the activation of dendritic cells that influence the adaptive response. This is an area of intense research focus and may uncover targets suitable for therapeutic interventions.

Less is known about some of the initiating steps that lead to celiac disease. How and when gluten sensitivity and development of autoimmunity first occur is unknown. The interplay between the innate responses and adaptive responses is likely

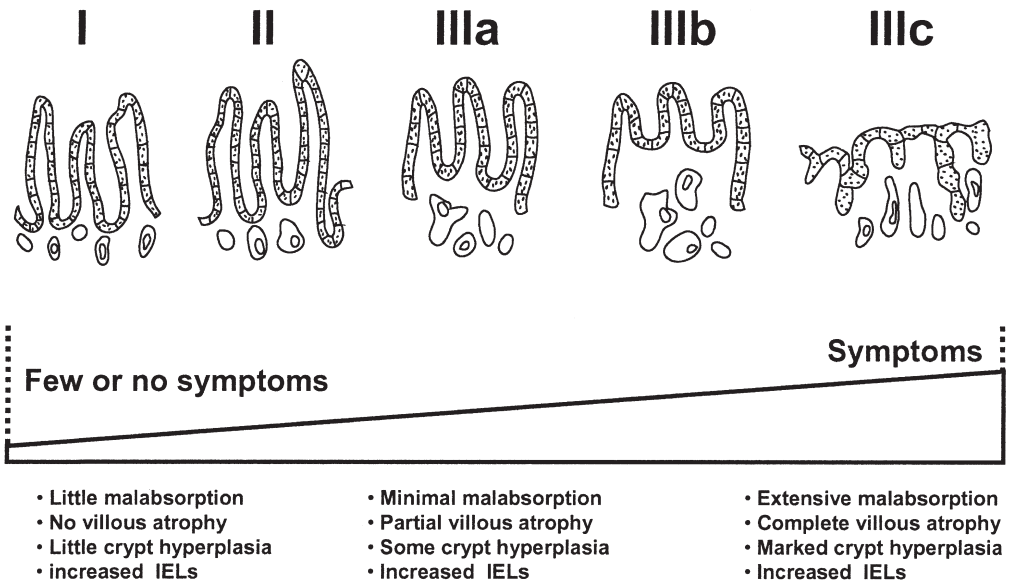


**Figure 1.** Spectrum of malabsorption and symptoms in celiac disease. The magnitude of malabsorption and symptoms in patients with celiac disease (*bottom*) often correlates with the extent of small intestinal mucosal injury as depicted schematically from I to IIIc according to the Marsh histologic damage score (also see Table 1).

crucial to the development of celiac disease and is the focus of much ongoing research. It has been hypothesized that, at least in some individuals, an insult such as an enteric infection or surgery or gluten itself may result in compromised epithelial barrier function and the initiation of intestinal inflammation. This would allow incompletely digested gluten peptides to be deamidated and to come into contact with an immune system able to respond because of the carriage and expression of the appropriate HLA class II molecules DQ2 or DQ8.

**tTG.** tTG is a ubiquitous enzyme found both within and outside of cells. It has many functions and physiologic roles. In celiac disease, it is involved in several processes. tTg is the target of an autoimmune humoral response that results in both secreted and circulating antibodies predominantly of the immunoglobulin (Ig) A isotype. It is the enzymatic deamidation by tTg of crucial glutamine residues in gluten peptides that make deamidated gluten peptides more antigenic than native gluten peptides. Finally, it has been suggested that tTG is important also in the destructive effect of $CD8^+$ cytotoxic cells on the epithelium.[10]

## Aim of the Technical Review

The aim of this technical review on celiac disease is to address specific areas of clinical importance relevant to practicing gastroenterologists and primary care practitioners who see and detect most cases of celiac disease. The major focus is on adults, although some data from studies on children are also included for completeness. The specific issues related to celiac disease in childhood have been recently addressed.[11]

## Methods

This technical review was conducted using standard systematic review methodology to address several key content areas regarding celiac disease: use of serologic testing in diagnosis, use of HLA-DQ2/DQ8 testing in diagnosis, prevalence of celiac disease in the general population and in groups of individuals presumed to be at increased risk for celiac disease, complications of celiac disease, benefits of a GFD, promoting adherence to a GFD, and maintaining adherence to a GFD. The specific methodology has been reported previously.[12]

The literature search is current and includes outcomes not covered in a prior report.[12] Citations identified by the search strategy underwent multilevel screening by 2 independent reviewers using predetermined forms detailing the inclusion and exclusion criteria. Included articles were assessed for quality using a design-specific instrument. The obtained data were extracted and statistically pooled if clinically and statistically appropriate. If statistical pooling was not possible, a qualitative description of the studies is presented. The reference list for this review is extensive and has been shortened to meet length requirements. We reference sections of the Agency for Healthcare Research and Quality report,[12] and the updated list in its entirety is available online (http://www.ahrq.gov/downloads/pub/evidence/pdf/celiac/celiac.pdf and http://www.ahrq.gov/clinic/celiacinv.htm).

## Diagnosis of Celiac Disease

The diagnostic approach to detecting celiac disease has undergone important changes in recent years. This reflects the development and application of serologic tests, particularly the EMA and tTG antibody tests, as an initial screen for this disease. Serologic tests are largely responsible for the recognition that celiac disease is not a rare disease. Moreover, with the recognition of a relatively high prevalence of celiac disease in the US population (~1:100) has come increased recognition of its broad spectrum of clinical presentations.[13–16] Despite the fact that positive serologic test results can be supportive of the diagnosis, small intestinal mucosal biopsy remains the gold standard for establishing the diagnosis of celiac disease. A diagnosis of celiac disease requires demonstration of characteristic histologic changes in the small intestinal mucosa, which are generally scored based on a system initially put forth by Marsh[15] and subsequently modified.[16] The histologic changes in the small intestinal mucosa can range from total to partial villous atrophy.[15,16] In some individuals, only more subtle changes of crypt lengthening with an increase in intraepithelial lymphocytes, or simply an increase in intraepithelial lymphocytes, are present. In routine practice, there is not a need for special stains such as staining for CD3 to detect the intraepithelial lymphocyte population. Mucosal changes can be patchy. Therefore, it is important to take multiple endoscopic biopsy specimens (ideally 4–6 biopsy specimens) from the proximal small intestine. Biopsy specimens should be of sufficient size, carefully oriented, and mounted villous side up to enable cross sectioning rather than tangential sectioning, because the latter can lead to misleading interpretations. Larger specimens can be obtained using a jumbo or a radial jaw biopsy forceps. Only a single biopsy specimen should be obtained with each pass of the biopsy forceps. It is important that the slides be reviewed by an experienced pathologist familiar with the spectrum of mucosal changes in celiac disease. Positive serologic test results may resolve and histologic findings may improve with the removal of gluten from the diet. Therefore, diagnostic tests should be performed before the initiation of gluten restriction. In addition, the extent of mucosal inflammation or architectural abnormality can be masked if individuals are taking corticosteroids or immunosuppressants. Although not all patients with celiac disease have positive serologic test results or significant symptoms, in those who do, it is anticipated that serologic test results will revert to normal over a period of 6 months to 1 year and symptoms will improve on a GFD. Notably, gluten challenge and a repeat biopsy are no longer required to establish the diagnosis of celiac disease in patients whose small intestinal biopsy specimen has the characteristic histologic appearance and in whom an objective response to a GFD is obtained. However, a gluten challenge with a subsequent biopsy does have a role in establishing the diagnosis in select clinical settings (eg, in those with a high suspicion for celiac disease, with a negative serologic test result, and started on a GFD without biopsy confirmation of disease).

The diagnosis is not always clear-cut. This is the case in those with minimal histologic findings, negative serologic test results, and repeated positive serologic test results but no apparent abnormalities on histologic examination. Histologic findings can also be misleading if the disease is patchy and an insufficient number of biopsy specimens were taken or if the biopsy specimen was poorly oriented and tissue sections were cut tangentially. Inflammatory changes in the mucosa can also be due to other causes.[17] Multiple biopsy specimens are best obtained from the second part of the duodenum or beyond. There

**Table 2.** Sensitivity and Specificity of Serologic Tests

| Analysis | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| IgA EMA-ME, adult | 0.974 | 0.957–0.985 | 0.996 | 0.988–0.999 |
| IgA EMA-ME, child | 0.961 | 0.945–0.973 | 0.974 | 0.963–0.982 |
| IgA EMA-HU, adult | 0.902 | 0.863–0.925 | 0.996 | 0.984–0.999 |
| IgA EMA-HU, child | 0.969 | 0.935–0.986 | ~0.99 | H[a] |
| IgA tTGA-GP, adult | ~0.90 | H[a] | 0.953 | 0.925–0.981 |
| IgA tTGA-GP, child | 0.931 | 0.888–0.959 | 0.963 | 0.931–0.980 |
| IgA tTGA-HR, adult | 0.951 | 0.918–0.981 | 0.983 | 0.971–0.996 |
| IgA tTGA-HR, child | 0.957 | 0.903–0.981 | 0.990 | 0.946–0.998 |

[a]Heterogeneity in analysis; best estimate provided.

is no accepted norm as to whether the histologic changes are interpreted as the most severe changes seen, the least severe changes seen, or the average degree of injury, although many publications grade the pathologic change by the most severe injury seen on any biopsy specimen.

There are other disease entities that can resemble celiac disease histologically. Most of these entities are either rare in the developed world, are suggested by the clinical history, or have distinguishing histologic findings on careful review of the biopsy samples. Furthermore, it is crucial that the dietary status of the patient at the time of biopsy be taken into account. Patients should undergo biopsy promptly after obtaining a positive serologic test result and should be instructed not to avoid gluten until after biopsy specimens are obtained. A gluten-reduced diet may reduce the severity of the lesion and hence impact pathologic interpretation. How long gluten must be reintroduced before biopsy specimens are taken can vary among individuals already on a GFD. A 4-week challenge with sufficient gluten to reproduce the symptoms is adequate in most. However, some patients may have very delayed responses, and it can take up to several years for relapse to occur.[18]

In some individuals, further evaluation with testing for the presence of specific HLA class II DQ alleles can help exclude the disease; if alleles that code for DQ2 or DQ8 are absent, the need for biopsy can be alleviated. As noted, a diagnosis of celiac disease and prescription of a GFD for life should not be made in the absence of compatible small intestinal histologic findings and irrespective of positive serologic test results.

## *Serologic Tests*

Widely available serologic tests used for detecting celiac disease include antigliadin antibodies (AGA), EMA, and tTG antibodies (tTGA). The diagnostic performance of these tests in various studies and clinical situations is examined in the following sections.[12] Many of the studies that were reviewed had important methodological limitations; therefore, strict inclusion and exclusion criteria were used. Threats to the validity of studies of diagnostic tests, and the justification for the exclusion criteria used herein, were reported previously.[12] The information provided is summarized in Table 2.

**EMA.** EMA is measured using an immunofluorescence technique with monkey esophagus or human umbilical cord as the tissue substrate. The resulting stained tissue is viewed under a fluorescence microscope to determine if the staining pattern is positive. As a result, this test is more time consuming and operator dependent than the others.

*IgA EMA performed using monkey esophagus as substrate.* The diagnostic performance of the IgA EMA performed using monkey esophagus (ME) as substrate in adults has been evaluated in several studies.[12] The pooled sensitivity was excellent at 97.4% (95% confidence interval [CI], 95.7–98.5), as was the pooled specificity at 99.6% (95% CI, 98.8–99.9). In children, IgA EMA-ME also demonstrated excellent performance, with a pooled sensitivity and specificity of 96.1% (95% CI, 94.5–97.3) and 97.4% (95% CI, 96.3–98.2), respectively.[12] In mixed populations of children and adults, studies showed specificities of greater than 98%. However, those studies had some variation in sensitivities. One study reported a very low sensitivity of 75%, while in the remainder the sensitivity ranged from 86% to 98%.[12]

*IgA EMA performed using human umbilical cord as substrate.* The specificity of the IgA EMA using human umbilical cord (HU) as substrate in adults was reported as 100% in nearly all the studies that met the inclusion criteria.[12,19] However, there was greater variability in the sensitivity, which ranged from 87% to 100%. The pooled sensitivity and specificity of this test were 90.2% (95% CI, 86.3–92.5) and 99.6% (95% CI, 98.4–99.9), respectively. Studies that assessed IgA EMA-HU performance in children reported some variability in specificity.[12] As a result, a pooled specificity was not calculated but is likely to be close to 100%. The pooled sensitivity in children was 96.9% (95% CI, 93.5–98.6). Two studies assessed IgA EMA-HU in a mixed-age population. The pooled sensitivity was 93% (95% CI, 88.1%–95.4%), while the specificity was 100% (95% CI, 97.5%–100%).

**tTGA.** tTGA is measured by quantitative enzyme-linked immunosorbent assay with guinea pig liver (GP) or human recombinant or red cell–derived tTG as the substrate.

*IgA tTGA-GP.* Studies of tTGA-GP in adults have marked variability in the reported sensitivity, which precludes statistical pooling. However, the overall sensitivity is likely to be close to 90%.[12] The pooled specificity was 95.3% (95% CI, 92.5%–98.1%). In children, the pooled estimates of sensitivity and specificity were 93.1% (95% CI, 88.8%–95.9%) and 96.3% (95% CI, 93.1%–98.0%), respectively.[12] Among studies that used mixed age groups, the pooled sensitivity and specificity were 93.7% (95% CI, 90.8%–96.7%) and 95.4% (95% CI, 92.7%–97.2%), respectively.

*IgA tTGA HU.* Most commercial tests for IgA tTGA now use human recombinant or red blood cell–derived tTG as substrate. In an adult population, the pooled estimates of the sensitivity and specificity of IgA tTGA-HU were 95.1% (95% CI, 91.8%–98.1%) and 98.3% (95% CI, 97.1%–99.6%), respectively. Among the studies in children, the pooled estimates of sensitivity and specificity were 95.7% (95% CI, 90.3%–98.1%) and 99.0% (95% CI, 94.6%–99.8%), respectively. In a mixed-age population, the pooled estimates of sensitivity and specificity were

90.2% (95% CI, 86.4%–93.0%) and 95.4% (95% CI, 91.5%–97.6%), respectively.[12,19] There does not appear to be a major difference between tests that use recombinant tTG and those that use tTG derived from red blood cells.[12] Overall, these studies demonstrate a specificity of IgA tTGA that is greater than 95% and a sensitivity in the range of 90%–96%. False-positive results of the IgA tTG-HU (eg, in patients with liver disease, congestive heart failure, arthritis, and inflammatory bowel disease) are less common than with the earlier-generation IgA tTG-GP tests, although there still may be differences in the sensitivity and specificity of test kits used by different commercial laboratories.

**IgA AGA.** IgA AGA by enzyme-linked immunosorbent assay predates the previously described serologic tests. Methodology for the conduct of this test has changed and improved over time, and along with other issues, such as different study populations and different test cutoff levels, has made the identified articles quite heterogeneous. However, the bulk of the data suggest that the specificity of the IgA AGA approximates 90%. Far greater variation exists in estimates of the sensitivity of this test. However, our best estimate would place the sensitivity in the 85%–90% range. Nonetheless, even if considering the sensitivity and specificity of this test to be in the low 90% range, the use of IgA AGA would still not be attractive in usual clinical practice owing to a very low positive predictive value (PPV) and the existence of alternative serologic tests with better diagnostic performance.[12]

### *Serologic Tests in IgA-Deficient Patients*

Selective IgA deficiency, the commonest human immunodeficiency, is 10–15 times more common in patients with celiac disease than in the general population, with a prevalence of 1.7%–3% in patients with celiac disease.[20–24] The reverse association is also the case, with a higher prevalence of celiac disease in IgA-deficient subjects (up to 8%).[25]

The importance of this association lies first in recognizing its existence and second in recognizing that because the standard EMA, tTGA, and AGA tests are IgA based, patients with both celiac disease and IgA deficiency cannot be reliably detected by these tests.[12]

In individuals who are not IgA deficient, the measurement of IgG AGA offers fair sensitivity and specificity (most studies in the 80%–90% range). Although IgG EMA and IgG tTG have excellent specificity in those individuals (up to 100%), their sensitivity generally has been less than 70%.[12] In contrast, in celiac disease, IgA deficiency appears to result in higher titers of IgG EMA, IgG tTGA, and IgG AGA,[26] and it appears that the sensitivity of IgG EMA and tTGA is close to 100% in IgA-deficient patients with celiac disease.[23,26,27]

The prevalence of IgA deficiency in celiac disease is sufficiently low, such that we do not consider the routine measurement of serum IgA levels along with IgA EMA or tTGA to be warranted as a first step toward diagnosis unless IgA deficiency is strongly suspected. In patients with a negative IgA EMA or IgA tTG but in whom celiac disease is still suspected, measurement of serum IgA levels is reasonable as a next step. If celiac disease is strongly suspected despite negative serologic test results, one can test for the presence of the disease-associated HLA alleles and, if present, proceed to small intestinal mucosal biopsy. Alternatively, it is reasonable to proceed directly to upper intestinal endoscopy and small bowel biopsy if the signs and symptoms that suggested celiac disease would otherwise warrant those procedures.

We recommend that, in the primary care setting, the IgA tTGA be used as the most efficient single serologic test for the detection of celiac disease. The inclusion of other tests in the panel, especially IgG AGA and IgA AGA, adds little to the sensitivity but a substantial economic cost to specificity if any positive result leads to further investigation.

### *Use of HLA-DQ2/DQ8 to Exclude the Diagnosis of Celiac Disease*

Approximately 25%–40% of the general population in the United States carry the HLA class II heterodimer HLA-DQ2 or HLA-DQ8, which reflects the presence of the DQ alleles DQA1*05 and DQB1*02 (DQ2) or DQA1*03 and DQB1*0302 (DQ8). However, almost all patients with celiac disease carry the DQ2 or DQ8 molecule.[12] DQA1*05 and DQB1*02 typically occur on the same chromosome (ie, in cis) in individuals with HLA-DR17, or one of these alleles is present on each chromosome (ie, in trans) in individuals who are HLA-DR11/DR7 or HLA-DR12/DR7. Individuals in each of these cases can form a DQ2 molecule associated with susceptibility to celiac disease. Approximately 95% of patients with celiac disease have HLA-DQ2, whereas the remaining ~5% have HLA-DQ8 in association with DR4. In Europe, a small number of patients with celiac disease have been noted to have only DQA1*O5 or DQB1*02, the latter usually being associated with HLA-DR7 heterozygosity or homozygosity. Of note, individuals homozygous for DR17 and thus homozygous for the DQ2 molecule associated with celiac disease comprise approximately 2% of the population but make up approximately 25% of all patients with celiac disease. Nonetheless, once the disease develops, the clinical course of the disease generally appears to be similar whether or not the disease develops, the clinical course of the disease generally appears to be similar whether or not 100%, 50%, or 25% of an individual's HLA-DQ molecules are DQ2.[28] The DQ alleles present in celiac disease are also found in 48%–65% of healthy relatives of patients with celiac disease and up to 73% of patients with type 1 diabetes mellitus (DM1), which is also associated with celiac disease.

Virtually all patients with celiac disease have the celiac disease–associated alleles mentioned previously at the DQA1 and DQB1 loci. Thus, the presence of those alleles provides a sensitivity of close to 100% for celiac disease and a very high negative predictive value for the disease (ie, if individuals lack the relevant disease-associated alleles, celiac disease is virtually excluded). HLA testing for the relevant DQ alleles can be a very useful adjunct in an exclusionary sense when the diagnosis based on other test results is not clear.[12] In contrast, given the marked prevalence of the celiac disease–associated HLA class II alleles in the general population,[12] the specificity of these alleles for the disease is poor. The specificity of HLA class II DQ and DR alleles is also low when the tested population is known to have a high prevalence of celiac disease, such as in those with DM1 or first-degree relatives of patients with celiac disease. Despite a higher prevalence of celiac disease in such patients, the poor specificity makes the PPV low.[29]

Someone using HLA testing in the context of disease susceptibility in families, for example, must have the resources available to provide genetic counseling to subjects.

### *Pitfalls of Relying on Serologic Test Results Without a Small Intestinal Mucosal Biopsy*

A small intestinal mucosal biopsy is the current gold standard for the diagnosis of celiac disease and must be used to confirm positive serologic test results before introduction of a lifelong dietary modification.[12] The importance of a biopsy relates to concerns regarding the sensitivity of serologic tests in certain clinical circumstances and the potentially low PPV of serologic tests in usual clinical practice.

Multiple studies have shown that the sensitivity of EMA, tTGA, or AGA is related to the grade of histologic damage in celiac disease.[15,16] This has been observed both at the initial diagnosis and in the setting of monitoring for adherence to a GFD with serologic testing. The identified studies outlined earlier in this report were consistent in demonstrating a high sensitivity of the serologic tests in patients with total villous atrophy, with a subsequent decrease in sensitivity as less severe histologic grades of celiac disease were considered.[12] The sensitivity of IgA EMA or tTG in patients with partial villous atrophy ranged from 89% to as low as 30%, while the sensitivity in patients with Marsh grade II lesions was less than 50%.[12]

The PPV of IgA EMA and tTGA is also of potential concern. These tests have reported specificities close to 100% in the identified studies, but unless the specificity is truly perfect in usual clinical practice (>99%), then the PPV can be low. For example, if the prevalence of celiac disease is 15% and the sensitivity and specificity are both 98%, the PPV will be 90% (90% of patients with a positive test result have celiac disease and 10% do not have celiac disease). Any decrease in the prevalence of celiac disease (note that the prevalence is 1% in the general population) or the specificity of the test will lead to further decreases in PPV, hence the absolute need for confirmatory biopsy. Stated in another way, the positive (49.0) and negative (0.02) likelihood ratios for these serologic tests are excellent. However, a clinician's pretest probability for a patient having celiac disease has to be greater than 35% for the post-test probability to be greater than 95%. Given our new understanding of the spectrum of celiac disease and the celiac iceberg, situations wherein the pretest probability of celiac disease is 35% or higher are unusual. Therefore, it is prudent to confirm positive serologic test results before making a diagnosis of celiac disease and before instituting lifelong dietary changes.

Nonetheless, we note that diagnosis by biopsy in itself is not a perfect gold standard in that the disease can be patchy and the histologic features are not unique to celiac disease. The diagnosis of celiac disease in patients with Marsh grade I or II lesions may need further supportive evidence, such as through serologic or HLA testing. Further, persistently positive celiac disease serologic test results in the presence of normal histologic findings may be an indicator of latent celiac disease.[12]

## Epidemiology

Celiac disease has been classified into 4 phenotypes,[30] as described in Table 3. "Classic" celiac disease is dominated by the symptoms and sequelae of gastrointestinal malabsorption. "Atypical" celiac disease is characterized by few or no gastrointestinal symptoms, with extraintestinal manifestations predominating.[30] Of note, atypical celiac disease is more prevalent than classic celiac disease, which could call into question the use of these terms. "Silent" celiac disease is used when asymptomatic individuals have villous atrophy on biopsy. They may also have positive serologic test results. "Latent" celiac disease is characterized by asymptomatic individuals with currently normal histologic findings on a gluten-sufficient diet who subsequently develop celiac disease or those with a prior diagnosis of celiac disease that responded to a GFD and retain normal mucosal histologic findings despite the long-term ingestion of gluten. These individuals are asymptomatic and may or may not have an increase in intraepithelial lymphocytes.

**Table 3.** Common Definitions of Celiac Disease

| | |
|---|---|
| Classic | Classic celiac disease is the most commonly described form. It describes patients with the classic features of intestinal malabsorption who have fully developed gluten-induced villous atrophy and other classic histologic features. These patients present because of gastrointestinal symptoms. |
| Atypical | Atypical celiac disease appears to be the most common form. These patients generally have little to no gastrointestinal symptoms but come to medical attention because of other reasons such as iron deficiency, osteoporosis, short stature, or infertility. These patients generally have fully developed gluten-induced villous atrophy. Because these patients are "asymptomatic" from the gastrointestinal perspective, a large number go undiagnosed. |
| Silent | Silent celiac disease refers to asymptomatic patients who are discovered to have gluten-induced villous atrophy. They are discovered after serologic screening or perhaps during endoscopy and biopsy for another reason. These patients are clinically silent in that they do not manifest any clear gastrointestinal symptoms or associated atypical features of celiac disease such as iron deficiency or osteoporosis. |
| Latent | Latent celiac disease represents patients with a previous diagnosis of celiac disease that responded to a GFD and who retain a normal mucosal histology or manifest only an increase in intraepithelial lymphocytes. Latent celiac disease can also represent patients with currently normal intestinal mucosa on a gluten-containing diet who will subsequently develop celiac disease. |
| Refractory | Refractory celiac disease represents patients with true celiac disease (ie, not a misdiagnosis) who do not or no longer respond to a GFD. Some of these patients develop complications such as ulcerative jejunoileitis or enteropathy-associated T-cell lymphoma. |

## Prevalence of Celiac Disease

### *Prevalence of Celiac Disease in the General Population*

Much of the data on the prevalence of celiac disease in the general population has come from western European countries, where celiac disease previously was believed to be more common than in other parts of the world, including the United States. However, it is now apparent that celiac disease is also common in the United States, Eastern Europe, and many other countries with the exception of Japan.[31–34]

The prevalence of celiac disease varies greatly across and within different countries (Scandinavian countries,[35–50] Italy,[51–61] the United Kingdom,[62–66] and other countries [Spain,[67] Republic of San Marino,[68] The Netherlands,[69,70] Swit-

zerland,[71] and Germany[72]). This variability reflects true population differences in the risk of celiac disease as well as differences in study design and screening strategies, including the choice of serologic tests and whether biopsy confirmation was performed.

The reported prevalence of celiac disease ranges from 1:658 (0.152%) to 1:37 (2.67%) by serologic testing and from 1:658 (0.152%) to 1:53 (1.87%) by biopsy. Among European studies, 4 reports found a prevalence of celiac disease of greater than 1:66 (1.5%) (United Kingdom,[64] Sweden,[36,49] and Germany[72]). An additional 6 studies showed a prevalence of between 1:100 (1.0%) and 1:66 (1.5%) (United Kingdom,[65] Sweden,[45] Netherlands,[50] Ireland,[66] and Finland[43,44]). Three of 8 studies conducted in children reported a prevalence of celiac disease of greater than 1:100 (1.0%) (Finland,[44] Sweden,[36] and The Netherlands[50]). These studies would suggest a potentially higher prevalence of celiac disease in these countries. However, other reports from these same countries showed a prevalence of less than 1.0%, including 4 studies from Sweden.[38,41,45,46]

Several studies on the prevalence of celiac disease in the general US population have been conducted. The largest of these found a prevalence of celiac disease in "not at risk" populations of 1:105 (0.95%) in adults, 1:322 (0.31%) in children, and 1:133 overall (0.75%).[73] In another study,[74] the prevalence of serologies suggestive of celiac disease was 1:250 (0.4%) by initial AGA testing followed by EMA confirmation (data from this study were also included in the first report[73]). In neither report were serologic test results confirmed by biopsy.

The prevalence of celiac disease in 9 Italian studies was similar to that reported in the United States, ranging from 1:500 (0.2%) to 1:93 (1.08%).[51,53,56–61,67] In 2 reports in children, the prevalence of celiac disease confirmed by biopsy was 1:106 (0.94%)[51] and 1:119 (0.84%).[61] These results are similar to that of another report in a population of mostly adult Italians of 1:126 (0.79%).[60]

Overall, in interpreting these reports, we found that those studies with the smallest sample sizes tended to produce both the highest and lowest prevalence of celiac disease. Further, a number of studies did not mandate biopsy confirmation or a proportion of the patients did not undergo biopsy. In the last instance, the investigators tended to report the prevalence of celiac disease in a screened population based only on those patients with positive serologic test results who agreed to undergo biopsy, therefore potentially underestimating the true prevalence because some of those with positive serologic test results who declined to undergo a biopsy would also be expected to have celiac disease. With these limitations in mind, the prevalence of celiac disease in Western populations, including in the United States, appears to be approximately 1:100 (1%), with a reasonable range of 1:80 to 1:140 (1.25% to 0.71%).

As described in the following text, there are a number of populations at high risk for celiac disease, and in some of those screening should be conducted routinely (eg, unexplained iron deficiency anemia [IDA]). In other high-risk categories (eg, first-degree relatives), only symptomatic individuals should undergo screening for celiac disease because current data do not support a clear outcome benefit for the early detection and treatment of asymptomatic individuals in those categories. Nonetheless, the physician may wish to engage in individual discussions with such patients regarding the benefits and consequences of testing for celiac disease.

### *Prevalence of Celiac Disease in Relatives of Individuals With Known Celiac Disease*

**First-degree relatives.** In 5 studies, the prevalence of celiac disease in first-degree relatives of patients with celiac disease was evaluated using small intestinal mucosal biopsy alone.[75–79] In these studies, the percentage of at-risk family members tested varied from 34%[77] to 100%,[76] and the specific biopsy criteria were either not reported[76] or implied some degree of villous atrophy.[75,78–80] The prevalence of celiac disease among these first-degree relatives undergoing intestinal biopsy was reported to be 5.5%,[76] 10.3%,[75] 10.7%,[79] 20%,[78] and 22.5%.[77]

The prevalence of celiac disease in first-degree relatives of patients with celiac disease was also evaluated in studies using initial serologic screening.[73,81–91] Confirmatory intestinal biopsy was performed on at least 80% of the subjects who tested positive by serology in half of the studies and in 100% of subjects in the others.[81–86] Serologic screening was performed with AGA alone in one study[81] or by EMA, either alone[86] or in combination with AGA,[82–85,87] in the other 6 studies. The prevalence of celiac disease varied from 4%[81] to 12%,[82] with a pooled prevalence of 7.6% (95% CI, 6.59%–8.67%). However, when Marsh grade I lesions were also considered in the diagnosis of celiac disease, the prevalence of celiac disease among first-degree relatives was reported to be 44.1%.[83] This finding may partially explain the higher prevalence of 20%–22.5% reported previously for the biopsy-only studies.

In 5 other studies of first-degree relatives,[73,88–91] confirmatory biopsy specimens were available in 9%[91] to 58%[88] of the cases, but the reported prevalence of celiac disease was based on the serologic results. EMA was used for serologic screening in all of these studies, either alone[73,90] or in combination with AGA[88,91] or tTGA.[89] The prevalence of celiac disease among these serology-tested first-degree relatives varied between 2.8%[91] and 4.5%.[73] The prevalence of celiac disease among first-degree relatives from families in which there were at least 2 index cases (sibling pairs) of known celiac disease or dermatitis herpetiformis was reported as 6.4%,[92] 9.4%,[88] and 17.2%.[89] The utility of testing for celiac disease in symptomatic first-degree relatives is clear, whereas there is currently little evidence to support screening in asymptomatic first-degree relatives.

**Other relatives.** One study from the United States[93] reported a prevalence of presumed celiac disease in 4.7% of 192 first-degree and second-degree relatives, based strictly on the EMA test. The prevalence for first-degree and second-degree relatives was not reported separately. Two other studies[73,86] provided data on the presumed prevalence of celiac disease in second-degree relatives. The EMA-based prevalence of celiac disease in those groups was 2.6% and 5.5%, respectively. In the last study, presumed celiac disease by serologic testing in relatives of sibling pairs was 19.5% in second-degree relatives and 17.0% in first cousins.[89] In this study, subjects were tested with EMA and tTGA, and the diagnosis was biopsy confirmed in 40% of the cases.

In summary, relatives of patients with celiac disease are at a higher risk for celiac disease than those in the general population. Based on studies, with relatively complete biopsy confirmation, the prevalence is close to 10% but may be higher if lesser histologic grades are also considered to represent celiac disease. Among relatives, the highest prevalence of celiac disease occurs in families with more than one affected relative, while

the prevalence when second-degree relatives are affected is lower (2.6%–5.5%) but still higher than that of the general population.

### *Prevalence of Celiac Disease in Patients With IDA*

IDA is commonly reported to be associated with celiac disease,[94–107] irrespective of whether patients have gastrointestinal symptoms.

In asymptomatic patients with IDA evaluated by serologic testing, the prevalence of celiac disease ranged from 2.3% to 5.0%.[96,98,102,103] Similarly, in studies assessing the causes of IDA, typically by both upper and lower endoscopy, the prevalence of celiac disease by biopsy was found to be between 2.8% and 8.7%.[95,100,105–107] In contrast, the prevalence of celiac disease in symptomatic patients with IDA ranged from 10.3% to 15% of the studied group, and in one small study of previously investigated patients with IDA, the prevalence of presumed celiac disease by AGA followed by EMA confirmation was 30%.[97]

In another small study, the prevalence of celiac disease in premenopausal women with IDA was assessed.[104] The overall prevalence of celiac disease in this population was 12.9% by tTGA and 8.5% after biopsy confirmation. Celiac disease was found in 1 of 22 women (4.5%) with heavy periods and 4 of 18 women (22%) with normal menstrual flow.

Celiac disease should be considered in any adult with unexplained IDA, including menstruating women. Duodenal biopsies should be performed on patients with IDA presenting for upper intestinal endoscopy.

### *Prevalence of Celiac Disease in Individuals With Low Bone Mineral Density*

Seven studies have assessed the prevalence of celiac disease in patients with low bone mineral density (BMD).[108–114] Six of these determined BMD using dual energy X-ray absorptiometry and appropriately defined osteoporosis by World Health Organization criteria.[108,110–114] One study used single-photon absorptiometry.[109] Each of these studies used serologic screening with biopsy confirmation of screen-positive patients. Three studies relied on AGA testing as the initial screen[108,109,111] followed by biopsy[109] or further confirmatory serologic testing with EMA[108] or tTGA[111] or a combination of EMA and tTGA.[112–114] The 3 most recent studies used well-conducted cohort designs with patients undergoing BMD measurements acting either as osteoporosis cases or controls.[112–114] Overall, in these studies, the prevalence of celiac disease in patients with osteoporosis varied from 0.9% to 3.4%. Two of the 3 cohort studies reported the prevalence of celiac disease in osteopenic patients to be 3.0%[113] and 1.2%,[114] while the prevalence of celiac disease in osteoporotic patients was 1.0% (1.7% in severe osteoporosis),[113] 2.1%,[114] and 3.4%.[112]

The true prevalence of celiac disease in patients with osteoporosis remains somewhat uncertain because of some methodological weaknesses of the identified studies and inclusion criteria for osteoporosis.[12,115] Nonetheless, a reasonable estimate would place it between 1% and 3.4%. The prevalence could be higher (5%) if patients with positive serologic test results did not undergo confirmatory biopsy.[108,112] Current evidence favors screening for celiac disease in individuals with premature-onset osteoporosis or a suggestion of metabolic bone disease.

### *Prevalence of Celiac Disease in Patients With Autoimmune Disorders*

Celiac disease appears to be more prevalent in several autoimmune disorders than in the general population. Additionally, some evidence suggests that the longer the exposure to gluten, the higher the risk of autoimmune disorders in patients with celiac disease. Ventura et al[116] found that autoimmune disorders were significantly more frequent in patients with celiac disease than controls (14% vs 2.8%), and the risk of autoimmune disorders appeared to increase with the duration of gluten exposure when age at diagnosis was used as a measure of years of exposure to gluten.

Because approximately 95% of patients with celiac disease carry HLA-DQ2 and the remainder mostly DQ8, it is reasonable to assume that the association between celiac disease and these autoimmune disorders is on the basis of these shared HLA susceptibility genes. However, for the increased prevalence of celiac disease to be explained on this basis, DQ2/DQ8 should be expected to act as a susceptibility gene for these other disorders, or the prevalence of DQ2/DQ8 in these other disorders should be higher than that seen in the general population. While this may be the case for DM1,[12] autoimmune thyroid disease,[117–119] and Addison's disease,[120] the situation is less clear for other celiac disease–associated conditions.

### *Prevalence of Celiac Disease in Patients With DM1*

There is extensive literature on the higher prevalence of celiac disease in patients with DM1 than in the general population.[29,72,117,121–159] Of note, both disorders can share the same HLA-DQ2/8 susceptibility alleles.

The identified studies initially screened the study population with one or more serologic tests, followed by biopsy confirmation in the majority of studies. A few studies did not confirm positive serologic test results[122,132,145]; in others, biopsy confirmation was performed in less than 75% of subjects.[121,123,129,138,146–149,152] The studies that reported biopsy criteria used partial villous atrophy, or a greater degree of histologic abnormality, to define celiac disease.

The minimum and maximum prevalence of celiac disease in DM1 by serologic testing in these reports was 1% and 12%, respectively, whereas the minimum and maximum prevalence of celiac disease by biopsy was 1% and 11%, respectively. Although not statistically significant, the prevalence range of celiac disease in adults was slightly lower than in children (1%–10% vs 3%–12%). Variability in the reported prevalence precluded statistical pooling of the results. However, the majority of studies clustered prevalence in the range of 2%–5% in adults and 3%–8% in children. Clinicians caring for patients with DM1 should be aware of the association with celiac disease and consider testing for celiac disease if symptoms occur (eg, unexplained hypoglycemia). If patients with DM1 present for upper endoscopy, small intestinal mucosal biopsies should be considered.

### *Prevalence of Celiac Disease in Patients With Autoimmune Thyroid Disease*

The prevalence of celiac disease in patients with autoimmune thyroid disease has been assessed in multiple studies.[160–172] These studies are consistent in reporting that celiac disease occurs in 1.5%–6.7% of these patients, with a pooled

estimate by biopsy of 3.0% (95% CI, 2.3–3.8). In one study, the investigators found that the prevalence of celiac disease was greater in those 65 years or older (3.6%) than those younger than 65 years (0.6%).[165] None of the other identified studies performed this analysis. A recent large genetic linkage study failed to demonstrate a single major locus associated with autoimmune thyroid disease,[173] suggesting a genetically heterogeneous disease. Nonetheless, other reports have found an increased prevalence of DQ2/DQ8 in autoimmune thyroid disease.[117–119] The data do not present a compelling rationale for the screening of patients with thyroid disease for celiac disease.

### *Prevalence of Celiac Disease in Patients With Liver Disease*

Celiac disease can be associated with mild asymptomatic elevations of transaminase levels found during routine blood testing. Celiac disease may also be found in patients with chronic liver disorders such as primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, and cryptogenic liver disease. Elevated transaminase levels may be the only manifestation of celiac disease, and the introduction of a GFD may correct elevated transaminase levels in these patients.[116,174,175] In the screening of patients with liver diseases, several studies indicate that tTGA, especially tTGA-GP, is less specific than EMA, particularly in those patients with more advanced liver disease.[174,176–182] The prevalence of celiac disease in patients with elevated transaminase levels of unknown cause has been reported to be between 1.5% and 9.0%,[183–185] between 2.9% and 6.4% in patients with autoimmune hepatitis,[186–188] and between 0%[187] and 6.0% in those with primary biliary cirrhosis.[174,177,178,187,189,190] The evidence is not as strong for primary sclerosing cholangitis, but it also appears that the prevalence of celiac disease is elevated in this disorder and is likely close to 1.5%.[179,190] One study assessed the prevalence of celiac disease among liver transplant recipients and found that 8 of 185 patients (4.3%) had celiac disease.[179] Of these patients, 3 had primary biliary cirrhosis, one had autoimmune hepatitis, and one had primary sclerosing cholangitis. Celiac disease may also be associated with nonalcoholic fatty liver disease. In a study of 59 patients with nonalcoholic fatty liver disease, 2 (3.4%) were found to have celiac disease.[182] Finally, one study using AGA testing suggested that the prevalence of celiac disease may be elevated in patients with "cryptogenic" chronic liver disease.[191] The reason for the association between celiac disease and these liver diseases is not understood and may differ among those diseases.[178] For example, primary biliary cirrhosis has been associated with DQ2 in some reports[192] but not in others,[178] suggesting that primary biliary cirrhosis is genetically heterogeneous, and the association with celiac disease may not be on the basis of DQ2/DQ8 alone. Clinicians need to be aware of these associations of celiac disease and have a low threshold for testing for coexistent celiac disease in patients with those liver diseases.

### *Prevalence of Celiac Disease in Patients With Other Disorders*

The prevalence of celiac disease in patients with Down syndrome has been evaluated in multiple studies showing evidence of a strong association. Studies that used AGA as the only screening test or those that used AGA with less than 90% biopsy confirmation were not considered for the pooled analysis. Overall, the prevalence of celiac disease in patients with Down syndrome ranged from 3% to 12%, with pooled estimates of 7.6% (95% CI, 6.63%–8.67%) by serologic testing and 5.5% (95% CI, 4.41%–6.16%) by biopsy.[193–209] These pooled data suggest that the risk of celiac disease in patients with Down syndrome is at least 5 times that of the average-risk population. This is further collaborated by a large UK cohort study of 1453 patients with Down syndrome and 460,000 controls that found the relative risk of celiac disease in patients with Down syndrome to be 4.7 (95% CI, 1.3–12.2) times that in controls.[210] Patients with Down syndrome with celiac disease have the HLA class II alleles coding for DQ2 and/or DQ8. However, the prevalence of DQ2/DQ8 in patients with Down syndrome is similar to that in the general population,[211] indicating that some unknown factor(s) are associated with the increased risk of celiac disease in patients with Down syndrome. HLA typing can be useful to help exclude the possibility of the future development of celiac disease in these patients. In individuals with Down syndrome who are unable to describe symptoms, screening should be offered.

The prevalence of celiac disease in patients with Turner's syndrome also appears to be higher than in the general population, with a range of 2%–10% and a pooled estimate of 6.3% (95% CI, 4.57%–8.64%).[212–216] As in Down syndrome, patients with celiac disease with Turner's syndrome are DQ2 positive, but the prevalence of DQ2 in patients with Turner's syndrome may not be higher than in the general population.[216] The prevalence of celiac disease may also be increased in patients with Williams syndrome, although limited data are available.[217,218] Symptomatic individuals with Turner's syndrome or Williams syndrome should be tested for celiac disease, with a low threshold for testing in the latter group who are unable to describe symptoms.

Celiac disease also appears to be associated with reproductive complications. A case-control study found that patients with celiac disease compared with controls had later menarche and fewer live births.[219] After the diagnosis of celiac disease, patients had similar numbers of births as controls, suggesting an initial lowered fertility related to celiac disease and an improvement after diagnosis that was presumably related to a GFD. The investigators also found higher rates of miscarriage in patients with celiac disease before diagnosis compared with controls. The prevalence of celiac disease in patients with unexplained infertility has been reported in several studies and also appears to be higher than that in the general population. In one series[220] and 4 case-control studies,[221–224] the prevalence of celiac disease was between 2.1% and 4.1% in women with unexplained infertility. The pooled relative risk of celiac disease in infertile women compared with controls was 3.7 (95% CI, 1.3–10.4).

Celiac disease has also been associated with other conditions, including ulcerative colitis, Crohn's disease, Addison's disease, IgA nephropathy, idiopathic epilepsy, occipital calcifications, and ataxia.[117, 225–229] Currently there is no evidence to support delaying the time of introduction of gluten into the diet of children in "at-risk" groups.

## Complications of Celiac Disease

### *Mortality*

Mortality associated with celiac disease has been assessed in several cohort studies[230–235] and a survey. Among the

cohort studies, included patients had biopsy-proven celiac disease, and the majority had symptomatic celiac disease. The death rate in patients with celiac disease was higher than that of a standardized population rate or of a control population in all but one study.[236] In the remaining studies, the standardized mortality rate (SMR; the ratio of the number of deaths observed in the studied patients with celiac disease to the number expected on the basis of age- and sex-specific rates in the region under study) was 1.9 to 3.4.[230–234] Corrao et al[231] found that the overall SMR did not differ by sex, age of diagnosis, or year of presentation over the baseline SMR of 2.0. However, the risk of death was higher among patients presenting with malabsorption (SMR, 2.5; 95% CI: 1.8–3.4), patients not adhering to a GFD as determined by clinical records (SMR, 10.7; 95% CI, 6.0–17.1) or on patient interview (SMR, 6.1; 95% CI, 4.2–8.6), and in the presence of a diagnostic delay (delay of 1–10 years: SMR, 2.6 [95% CI, 1.6–4.1]; delay >10 years: SMR, 3.8 [95% CI, 2.2–6.4]).[237] No excess mortality was seen in patients with mild or asymptomatic celiac disease. Causes of death showed an excess risk of death from malignancy (SMR, 2.6; 95% CI, 1.7–3.9), with non-Hodgkin's lymphoma (NHL) accounting for two thirds of the cases of malignancy.

In 2 studies, the risk of death was greatest in the first year[231] and the first 4 years[230] after diagnosis. In another study, the risk of death from malignancy was higher in those on a regular diet compared with those on a GFD,[235] and the risk of death overall was higher in those who did not respond to a GFD compared with those who did.[232] Among the reported studies, the risk of death from cancer was not limited to NHL but also included other cancers, including cancer of the esophagus, stomach, pancreas, liver, bile ducts, small bowel, and pleura as well as melanoma and leukemia.

### *Lymphoma*

Celiac disease has been associated with an increased risk of lymphoma, but the magnitude of that risk appears to be lower than previously reported. Several sources of bias might explain this difference and also apply to the mortality data described previously. Firstly, malignancies may be more frequently diagnosed within the 1- to 3-year period following the diagnosis of celiac disease because the presence of a malignancy can precipitate the diagnosis of celiac disease and, conversely, the investigations involved in the diagnosis of celiac disease can uncover an occult or overt malignancy. This fact is particularly important because, in the case of a condition as rare as gastrointestinal lymphomas, the inclusion of just one case can greatly inflate the magnitude of risk compared with that of the general population. Other important sources of bias are the means of ascertaining the diagnosis of celiac disease as well as that of the malignancy itself, the accuracy of the reported incidence of lymphoma in the control population, and the representativeness of the celiac disease patient population.

Although celiac disease was initially associated with enteropathy-associated T-cell lymphoma, patients with celiac disease are also at increased risk for other types of NHL, both intestinal and extraintestinal. A recent review of all 56 cases of incident lymphomas occurring in a Swedish cohort of 11,650 patients with celiac disease showed that the majority (57%) were not intestinal T-cell lymphomas, that the risk of B-cell NHL was also increased (standardized incidence ratio [SIR], 2.2; 95% CI, 1.2–3.6; SIR is the ratio of the incidence of lymphoma observed in the studied patients with celiac disease to the incidence expected on the basis of age- and sex-specific rates in the region under study over the study period), and that the risks of intestinal and extraintestinal NHL were both increased (SIR, 24 [95% CI, 16–34] and 3.6 [95% CI, 2.3–5.2], respectively).[238]

The majority of published reports show that the SIR of NHL in patients with celiac disease compared with the general population varies between 2.7 and 6.3,[230,239–245] with the exception of one earlier report by Holmes et al. This study of a British cohort of patients with celiac disease followed up between 1941 and 1985 found the SIR of NHL to be 42.7.[246] In this study, although malignancies diagnosed within the 1-year period following the diagnosis of celiac disease were excluded, it could be hypothesized that referral bias could explain the higher SIR. However, as suggested by Askling et al,[241] it is also possible that there is an actual shift in the risk of lymphoma in celiac disease over time. These investigators observed, in a cohort of 11,019 Swedish patients with a discharge diagnosis of celiac disease, a significant decrease in the incidence of NHL over a 25-year period (*P* for trend, .025).

## Expected Benefits of a GFD

### *Protection From NHL*

Compliance with a GFD is likely protective against NHL in patients with celiac disease. Holmes et al reported a significant risk reduction of NHL in patients on a strict GFD (SIR, 44.4) versus those who did not adhere to a GFD (SIR, 100).[246] Others reported that a cohort of 383 patients with celiac disease with a very high prevalence of strict adherence to a GFD did not have a significantly increased risk of NHL compared with the general population (SIR, 2.66; 95% CI, 0.07–14.8).[242] Also, a recent prospective study of 1104 patients with dermatitis herpetiformis from Finland showed that those who developed NHL were less likely to have adhered to a strict GFD than age- and sex-matched controls with dermatitis herpetiformis.[247]

Despite the increased risk, NHL remains a relatively rare entity. In a prospective study of 381 patients with biopsy-proven celiac disease, Green et al reported a total of 9 NHLs, occurring at any time before or after the diagnosis of celiac disease, leading to an attributable risk of NHL from celiac disease of 120.2 cases per 100,000 patient-years.[243]

### *Effects on Body Composition, Anthropometrics, and IDA*

At diagnosis, adult patients with celiac disease have lower weight, height, body mass index (BMI), fat mass, and lean mass compared with controls without celiac disease. In contrast to men, women in one study showed no difference in height or BMD compared with controls, although women diagnosed as adults had lower BMD.[248] After as long as 12 months on a GFD, body weight, BMI, fat mass, bone mass, and triceps skin fold thickness increased significantly.[249] Patients adhering to a strict GFD consumed fewer calories than noncompliers but showed a trend toward greater improvements in the body composition measures.[249]

Similarly, in one study, children at diagnosis of celiac disease had lower weight, lean mass of limbs, fat mass, and bone mineral content than control children, but height, BMI, lean mass, and ratio of lean mass to height did not differ from

controls.[250] In another study, the height, bone mineral content, arm muscle area, triceps skin fold, subscapular skin fold, and fat area index were significantly lower in patients with celiac disease than in controls at baseline, while BMI and weight-for-height index were not different.[251] A GFD resulted in improvement of all the listed measures,[250–252] but the improvement in height did not reach control levels.[251]

A GFD has also been shown to improve nutritional and biochemical status, including improvements in IDA.[12,115] There is compelling evidence that treatment of symptomatic celiac disease results in substantial improvement in nutritional parameters.

### *Effects in Patients With DM1*

The benefits of a GFD on short-term outcomes in patients with DM1 with celiac disease have not been conclusively demonstrated. At baseline, patients with celiac disease and DM1 are usually reported to have a lower weight standard deviation score (Weight SDS = [Weight − Mean Weight]/SD, where mean weight and weight SD are derived from age and gender controls in the population) and BMI SDS compared with DM1 controls without celiac disease,[155,158,253,254] although similar height, weight, and BMI SDS at baseline have been reported.[255] Hemoglobin $A_{1c}$ levels in patients with DM1 and celiac disease have been reported to be lower,[254] similar,[253,255] or somewhat higher[158] than in control patients with DM1 at baseline. One study reported higher baseline mean ambulatory blood glucose levels in patients with DM1 and celiac disease compared with DM1 controls (12.0 mmol/L [216 mg/dL] vs 9.9 mmol/L [178.2 mg/dL]; $P < .05$) and a worse measure of diabetic brittleness and percent time with glucose level less than 3.9 mmol/L (70.2 mg/dL), but these did not reach statistical significance.[158]

After as long as 12 months of following a GFD, the studies initially reporting lower body index scores in patients with DM1 and celiac disease demonstrated improvements in BMI[253,254] and height SDS,[156] while those with BMIs similar to controls showed no further improvement.[255] A GFD did not result in a statistical improvement in hemoglobin $A_{1c}$ levels in 5 studies.[156,253–256] Lastly, insulin requirements appeared similar at baseline and tended to increase after starting a GFD.[253,254]

### *Effects on Low BMD and Osteoporosis*

Patients with celiac disease appear to have a higher prevalence of fractures than controls,[115,257–260] with the most common site being the wrist (odds ratio, 3.5; 95% CI, 1.8–7.2).[258] However, not all studies have shown this increased prevalence of fractures,[259,261,262] although the negative studies can be criticized because of a small sample size or for considering only fractures requiring hospitalizations.

In a large study, the hazard ratio was 1.3 for overall fractures (95% CI, 1.16–1.46), 1.9 (95% CI, 1.2–3.02) for hip fracture, and 1.77 (95% CI, 1.35–2.34) for wrist fracture.[259] The fracture risk differs with the phenotypic presentation of celiac disease. Moreno et al[260] found an increased number of fractures in the peripheral skeleton for classically symptomatic subjects compared with controls but did not find an increased number of fractures in the subjects with subclinical or silent celiac disease.

BMD is used as a surrogate outcome for fractures in short-term studies. However, it does not give a true volumetric measure and therefore may not be an accurate reflection of bone mass in children. Further, studies of osteoporosis therapies in postmenopausal osteoporosis have shown that there may not be a direct correlation between fracture reduction and increases in BMD.[115] The identified studies have consistently shown an increased prevalence of low BMD in patients with celiac disease compared with controls.[115] In one study, 40% of patients with celiac disease had osteopenia and 26% had osteoporosis.[115,263] In another, the prevalence of severe osteopenia, as defined by a Z-score less than −2, was 15% at the spine, 9% at the femoral neck, and 22% at the forearm, while the prevalence of mild osteopenia (defined as $-2 \leq Z < -1$) was 23% at the lumbar spine and 24% at the forearm.[115,264] A recent systematic review found that patients with untreated celiac disease had a mean Z-score of −1.42 and a hip Z-score of −1.14.[265]

Secondary hyperparathyroidism occurred in 27% of subjects with celiac disease.[264] These patients had lower BMD than patients with celiac disease without hyperparathyroidism at baseline, but the improvement in BMD on a GFD was greater in those with hyperparathyroidism.[266] BMD was also found to be lower in patients with villous atrophy (Marsh grade III or IV) compared with those with less histologic severity.[115, 266]

The treatment of celiac disease with a GFD resulted in improvements in BMD among the identified studies.[263,267–271] Improvements were seen in total body, lumbar spine, and femoral neck BMD, with the greatest improvements appearing in the first years of the GFD.[115] Improvements in BMD were also observed in children.[251,272]

## Promoting Adherence to a GFD

The treatment of celiac disease is lifelong adherence to a GFD. The preceding sections have discussed the benefits of identifying and treating patients with celiac disease. However, changes in dietary habits are difficult to maintain, and there are many barriers to continued compliance with a GFD. Adding to the difficulty of assessing any proposed intervention is the lack of certainty as to how best to measure compliance with a GFD.

Existing evidence suggests a positive correlation between parental socioeconomic status, education, and knowledge of celiac disease and the compliance of their children.[273,274] Compliant children may also have a better knowledge of celiac disease than those who are noncompliant. Improved knowledge in adults also appears to correlate with compliance.[275] It is therefore reasonable to suggest that interventions designed to improve knowledge about celiac disease and about the GFD, and specifically how to identify gluten-containing products, would likely improve compliance with a GFD. Improving knowledge regarding gluten-containing food products and additives would also likely improve self-confidence in choosing gluten-free foods.[275] Improved knowledge of outcomes of untreated celiac disease may also improve compliance. Membership in a local celiac society appears to be an effective means of promoting compliance with a GFD.[275] This is not surprising because such organizations provide patients with celiac disease with improved knowledge regarding their disease and the intricacies of the GFD and also provide emotional and social support opportunities. However, membership in a support group may correlate with a more motivated patient. One study[276] demonstrated lower rates of compliance in children detected by screening as compared with those diagnosed on the basis of symptoms. Another study suggested that children diagnosed at the age of 4 years or younger had greater compliance than those

diagnosed after age 4 years or in adulthood.[277] This suggests that early diagnosis may be an intervention to promote adherence to a GFD. Follow-up of celiac disease is necessary to detect and manage noncompliance.

## Monitoring Adherence to a GFD

Patients with celiac disease should be evaluated at regular intervals by a health care team including a physician and a dietician. These visits can be used to assess, by history, a patient's compliance with a GFD and to reinforce the importance of such compliance. Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. Symptom improvement alone may not offer an accurate assessment of adherence to a GFD as judged by interview or by biopsy,[278] and this becomes more problematic as less symptomatic patients with celiac disease are diagnosed. Repeat serologic testing after 6 months or more on a GFD can be helpful in assessing histologic improvement and compliance with a GFD. However, the sensitivity of the serologic tests decreases with lower Marsh grades of histologic severity; therefore, the serologic test results tend to become negative as the histologic findings improve and may not reflect a return to normal histology.[279–283] Nonetheless, in general, monitoring adherence to a GFD with serologies (ie, tTGA or EMA) can distinguish between compliers and noncompliers.[284–286] Whereas serologic testing appears to be sensitive to continuous major dietary indiscretions or after a prolonged gluten challenge, its sensitivity for minor dietary indiscretion can be low.[287–289] In children, histologic improvement on a GFD appears to occur quickly and more completely,[290] while in adults this improvement is slow, often taking more than 2 years,[280] and frequently is incomplete.[291,292] This lack of complete improvement does not appear to be explained on the basis of dietary noncompliance alone.[293] Serologic testing in children[294–296] may better represent the mucosal state than in adults, and negative serologic test results seem to be a better marker of the absence of villous atrophy. Therefore, monitoring adherence by clinic visits and serologic testing appear to be a reasonable approach in children. In adults, this approach is also reasonable, with the understanding that negative serologic test results do not necessarily mean improvement beyond severe subtotal or total villous atrophy.[281–283,289]

## Continued or Relapsing Symptoms in Treated Celiac Disease

Patients with known celiac disease can continue to have or redevelop symptoms despite being on a GFD. It is important to review the original diagnosis to ensure that it is accurate, and a repeat small intestinal biopsy may be indicated in patients with a poor response to a GFD. These symptoms may be due to incompletely healed celiac disease, an associated condition, a complication, or a second unrelated diagnosis.[297] Persistent or intermittent symptoms due to deliberate or inadvertent ingestion of gluten are commonly reported, and the most common cause of continued or relapsing symptoms is inadvertent gluten ingestion.[298] This may be detected by persistent positive serologic test results and by direct review of the dietary history. If gluten ingestion is not revealed, other entities such as microscopic colitis, irritable bowel syndrome, pancreatic exocrine insufficiency, bacterial overgrowth, and disaccharidase deficiency should be considered.

### *Refractory Celiac Disease*

Refractory celiac disease can be defined as severe villous atrophy associated with severe malabsorption that either does not or no longer responds to a GFD. It is possible that some cases of refractory sprue are not associated with gluten sensitivity, and other treatable forms of enteropathy must be excluded. The symptoms should be those that can readily be ascribed to enteropathy such as frank malabsorption and are often associated with hypoalbuminemia and malnutrition. Whereas primary failure to respond to a GFD may raise the possibility of an alternative cause of enteropathy, circumstantial evidence for celiac disease may be obtained by the presence of tTGA or EMA antibodies, the carriage of the appropriate celiac disease susceptibility alleles, a family history of celiac disease, or perhaps a partial response to gluten restriction. Other entities such as autoimmune enteropathy, common variable immunodeficiency syndrome, tropical sprue, and eosinophilic gastroenteritis should be considered. Other causes of continued symptoms in confirmed celiac disease should also be tested and treated.[297] Refractory celiac disease has a predilection for older patients and perhaps the carriage of a double dose of DQ2.[299] The disorder has been divided into 2 distinguishable types. Both types have chronic inflammation of the small intestine similar to untreated celiac disease except that the inflammation occurs in the absence of gluten. A positive tTGA may reflect continued ingestion of gluten because the tTGA frequently reverts to normal in refractory celiac disease if patients are on a GFD. The first type of refractory celiac disease has an expansion of phenotypically normal intraepithelial lymphocytes. These patients usually respond to corticosteroids and/or immunosuppression. The second type of refractory celiac disease is associated with a clonal expansion of intraepithelial lymphocytes. These intraepithelial lymphocytes are T cells that bear an unusual phenotype in that they express the CD3$\epsilon$ but lack the expression of CD4, CD8, and the $\beta$ chain of T-cell receptor.[300] These clonally expanded cells appear to be driven by interleukin-15 secreted by the epithelial cells, which can drive the proliferation of these cells in a manner that becomes independent of gluten stimulation. Identifying the clonal expansion of the intraepithelial lymphocytes that may presage lymphoma can be done by demonstrating an expanded intraepithelial lymphocyte population that lacks CD4, CD8, and T-cell receptor $\beta$ chain.[301]

### *Treatment of Refractory Celiac Disease*

Management often requires nutritional support, with active management for deficiency states, especially the often-advanced bone disease, in the face of continued malabsorption and may require nutritional support with total parenteral nutrition. Data on the treatment of cases of refractory celiac disease have not necessarily differentiated between both types of refractory celiac disease or ruled out alternative causes of enteropathy or symptoms. Occasionally, patients will respond to the removal of food proteins other than gluten.[302] Corticosteroids, including oral budesonide, have been used and frequently will suppress the inflammation. In those who have an unsatisfactory response to corticosteroids or unacceptable dose-related side effects, azathioprine may be beneficial.[303] The use of immunosuppressants and corticosteroids in these circumstances is often necessary but also fraught with risks of possible complications. Outcomes are quite uncertain, and reports are

largely anecdotal. The understanding of the immunopathogenesis of refractory celiac disease has provided some potential targets for intervention, such as blocking interleukin-15 with anti–interleukin-15 monoclonal antibodies.

In summary, identifying patients with celiac disease and making the diagnosis with the least possible delay appears to have a variety of health benefits for these patients. Making the diagnosis at a young age, educating patients and parents, and utilizing a multidisciplinary approach to patient management and follow-up would also be expected to improve compliance and patient outcomes.

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